REMARKS

Claims 8-9, 11-17, and 24-34 are pending in the present application. Claims 8, 11, 12, 24-27, 29, and 31 are amended herein. Upon entry of the amendments, claims 8-9, 11-17, and 24-34 will remain pending.

No new matter is added with the amendments. The amendments to claims 8, 24, and 29, which recite that the antibody suppresses leukocyte-leukocyte adhesion, are supported, for example, by page 4, lines 8-13. The amendment to claim 24 regarding suppressing HIV-induced cell fusion is supported, for example, by Example 2, which starts on page 20, and Example 3, which starts on page 22. The amendment to claims 25 and 27 are typographical in nature, and therefore do not add new matter. The amendment to the second full paragraph of page 5 of the application, as well as to claims 11, 12, 26, and 31, which enter the ATCC cell line number for a cell line that produces monoclonal antibody H52, are supported by the attached declaration of Applicant's agent, Lisa A. Haile. Accordingly, entry of the amendments is respectfully requested.

A. Rejection Under 35 U.S.C. 112, First Paragraph (Enablement)

The rejection of claim 24 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is respectfully traversed. The Office Action alleges that the invention of claim 24 is not enabled because no working examples of a method of ameliorating AIDS are presented. Furthermore, the Office Action alleges that the invention of claim 24 is not enabled because the invention would require excessive experimentation because the art allegedly demonstrates the failure of others in this field. Regarding the examples of ongoing clinical trials of immunotherapy for the treatment of AIDS presented by the Applicant in the Preliminary Amendment filed July 16, 2003, the Office Action alleges that these trials are not an enabling disclosure at the time of the instant application because they are ongoing and the application was filed in 1989.

Applicant respectfully disagrees with the allegation that the specification does not teach a skilled artisan how to ameliorate an immune response mediated disorder selected from AIDS, autoimmune disease, and graft rejection. However, to expedite issuance of the present application, Applicants have amended claim 24 to recite that the method is directed to a method of suppressing HIV-induced cell fusion. Example 2, which begins on page 20, and Example 3, which begins on page 22, illustrate the use of antibodies that suppress intercellular leukocyte adhesion to block HIV-mediated cell fusion. Therefore, the present invention teaches a skilled artisan how to make and use the claimed methods of suppressing HIV-induced cell fusion. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

B. Rejections Under 35 U.S.C. § 102

The rejection of claims 8, 9, 11, and 13-15 under 35 U.S.C. § 102(e) as allegedly being anticipated by Arfors (U.S. Patent No. 4,797,277), is respectfully traversed. To anticipate an invention, each and every element of a claim must be found in a single prior art reference. MPEP § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628,631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Office Action alleges that Arfors discloses methods for reperfusion therapy of a mammalian organ that include the step of administering systemically to the organ, a therapeutically active amount of an antibody preparation having specificity for a leukocyte adhesion complex (LAC) epitope that is responsible for leukocyte-endothelial cell adherence. Furthermore, the Office Action alleges that Arfors discloses that reperfusion-induced tissue damage occurs in clinical conditions such as organ transplantation, which allegedly is a graft. Therefore, the Office Action asserts that Arfors inherently discloses methods for ameliorating graft rejection. Finally, the Office Action cites previous assertions in prior Office Actions in this case, which allege that by teaching a method for preventing ischemia/reperfusion injury, Arfors teaches methods for ameliorating an immune response mediated disorder.

The claimed inventions of claims 8, 9, 11, and 13-15 as amended, are directed to a method of ameliorating an autoimmune disease or graft rejection in an animal by administering a

monoclonal antibody capable of suppressing intercellular leukocyte-leukocyte adhesion. As stated in the Office Action, Arfors discloses methods for reperfusion therapy by administering an antibody preparation having the specificity for an LAC-epitope that is responsible for *leukocyte-endothelial* cell adherence. (See e.g. Arfors Abstract, Col. 2, lines 56). In fact, Arfors states in the first paragraph of the section entitled "THE INVENTION" that "The objective of the present invention is an improved method for reperfusion therapy. *Its ultimate goal is to selectively prevent leukocytes from biospecifically adhering to vascular endothelial cell*s in injured tissue..." (Arfors, Col. 2, lines 50-53)(emphasis added). Furthermore, Arfors chose antibody 60.3, because it was known to block leukocyte adherence to endothelial cells (Arfors, Col. 2, lines 24-27). Thus, Arfors teaches away from the invention of claims 8-9, 11, and 13-15, because these claims are directed to methods that include administering a monoclonal antibody capable of suppressing intercellular *leukocyte-leukocyte* adhesion. Therefore, Arfors does not teach all of the claim elements.

Furthermore, Arfors is silent with respect to the element of claim 11, wherein the monoclonal antibody has the specificity of the monoclonal antibody produced by ATCC HB 10160 (H52). The antibody disclosed in Arfors, 60.3, binds to a different epitope than the monoclonal antibody produced by ATCC HB10160 (H52). This fact is evidenced by Figure 9 of Hildreth et al. (Molecular Immunology, Vol. 26, pages 1155-1167 (1989) (EXHIBIT B of the declaration of Dr. Hildreth (see below))), which shows that an anti-idiotype antibody directed against H52 does not bind to antibody 60.3. Therefore, Arfors does not disclose a monoclonal antibody that has the binding specificity of the monoclonal antibody produced by ATCC HB 10160 (H52).

Further evidence supporting the conclusion that the 60.3 antibody disclosed in Arfors et al. is not a monoclonal antibody that has the binding specificity of the monoclonal antibody produced by ATCC HB 10160 (H52), is provided by the accompanying Declaration of the inventor, Dr. Hildreth, submitted during the prosecution of parent application 08/200,491. The Declaration provides experimental data showing that antibody H52 binds to a unique epitope as

compared with other known CD18 antibodies. The experiments disclosed in the declaration show the following:

First, when H52 (i.e. the monoclonal antibody produced by ATCC deposit 10160) was used on an affinity column and spleen extracts were passed through the column, only 2 proteins were retained, LFA-1 alpha (CD11a) and beta subunits (CD18) (lane 2, Figure 1, Micklem, et al., 1987). When other antibodies such as MHM.23 were similarly used on affinity columns, all members of the LFA-1 family were retained, including LFA-1 alpha (CD11a), Mac01 alpha (CD11a), and p150 alpha (CD11c), all of which associated with CD18 (lane 1, FIGURE 1, Micklem, et al., 1987). This data shows that H52 dissociates the Mac-1 and p150/95 subunits but not the subunits of LFA-1. This phenomenon had not been reported for any other anti-CD18 antibodies. Second, when a monoclonal anti-idiotype antibody (AIM.6) was produced against the combining site of H52 and tested for binding to a variety of other CD18-specific antibodies, the AIM.6 antibody bound only to H52 and its companion antibody H5B9 (Hildreth and Hyman, 1989; FIGURE 9). H52 and H5B9 recognize the same unique epitope as determined in competitive binding studies. These results show that not all inhibitory anti-CD18 monoclonal antibodies carry the AIM.6 idiotope.

Third, the inventor has found that H52 recognizes the beta subunit after elution from affinity columns with high pH (Hildreth and August, 1985). High pH results in the separation of alpha and beta subunits of LFA-1. It appears that all function-inhibiting anti-CD18 antibodies except H52, no longer bind to CD18 after separation of subunits. The results of the above experiments show that H52 recognizes a unique epitope on CD18. Those of skill in the art were not in possession of H52 or antibodies having the specificity of H52 (i.e. the monoclonal antibody produced by ATCC deposit 10160), prior to Applicant's priority date. Therefore, since Arfors does not disclose all of the claim elements, Arfors cannot anticipate the claimed methods. Accordingly, reconsideration and withdrawal of the rejection of claims 8, 9, 11, and 13-15 under 35 U.S.C. § 102(e) are respectfully requested.

C. Rejections Under 35 U.S.C. § 103(a)

The rejection of claims 8, 9, 11-17 and 24-34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Arfors in view of Springer et al., Hildreth et al., and Pastan et al. is respectfully traversed. To establish a prima facie case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim elements. MPEP § 2142; In re Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). Regarding Applicant's prior assertion that none of the cited references teaches or suggests ameliorating AIDS, an autoimmune disease, or graft rejection, the Office Action alleges that it would have been obvious to combine the teachings of the prior art and to produce conjugates that include anti-LAR-beta chain specific monoclonal antibodies and cytotoxic moieties, to treat autoimmune diseases and organ transplantation.

As discussed above, Arfors is silent with respect to an antibody that suppresses intercellular leukocyte-leukocyte adhesion, an element that is present in the rejected independent claims. All of the other references cited in the Office Action are silent as to suppressing leukocyte-leukocyte adhesion as well. Springer, et al. disclose methods relating to the use of proteins (but not antibodies) for treating an autoimmune disease or an allograft rejection. Springer et al. generally describe antibodies specific for LAC components and the use of such antibodies for diagnostic purposes, but do not teach or suggest the use of such antibodies to ameliorate an immune response mediated disorder. Instead, Springer et al. describe the use of the polypeptide components of LAC (e.g., LFA-1), including peptides thereof, to treat an immune disorder (see page 12).

Hildreth et al., like Arfors and Springer et al., is silent as to suppressing leukocyte-leukocyte adhesion. Hildreth et al. describes subunit specific monoclonal antibodies, but is silent with respect to suppressing leukocyte-leukocyte adhesion. Pastan et al. relates to using immunotoxins to treat certain diseases by killing cells. Pastan et al. is also silent with respect to suppressing leukocyte-leukocyte adhesion. Therefore, the cited references, either individually or

when combined, do not teach a method that involves administering a monoclonal antibody capable of suppressing intercellular leukocyte-leukocyte adhesion.

Regarding claims 11, 12, 26, and 31, wherein the monoclonal antibody has the specificity of the monoclonal antibody produced by ATCC HB 10160 (Claims 11, 26, and 31) or is produced by ATCC HB10160 (Claim 12), Arfors, as discussed above, does not disclose a monoclonal antibody that has the binding specificity of the monoclonal antibody produced by ATCC HB 10160 (H52). Furthermore, as discussed above, Springer, et al. describes methods relating to the use of proteins (but not antibodies) for treating an immune response mediated disorder such as allograft rejections. Springer et al. generally describes antibodies specific for LAC components, but does not disclose an antibody that has the specificity of the monoclonal antibody produced by ATCC HB 10160. In addition, as discussed above, Pastan et al. relates to using immunotoxins to treat certain diseases by killing cells. As such, Pastan et al. is also silent with respect to a monoclonal antibody that has the specificity of the monoclonal antibody produced by ATCC HB 10160.

Regarding Hildreth et al., this reference does not render the claimed invention of claims 11, 12, 26, and 31 obvious under 35 U.S.C. §103 because it does not provide an enabling disclosure of an antibody that has the specificity of the monoclonal antibody produced by ATCC HB 10160. References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public (In re Payne, 203 USPQ 245, 255 (CCPA 1979)). One of skill in the art would not be able to practice the present invention, which uses an antibody with the specificity of antibody H52, based on the teaching of Hildreth et al., or the combination of cited references. Hildreth et al. discloses some of the specificity of the monoclonal antibody, however the reference does not teach one of skill in the art how to make the claimed invention. For example, Hildreth et al. provides insufficient detail for both immunization and screening protocols required to produce a monoclonal antibody with the specificity of H52.

With respect to claim 24 and claims dependent therefrom, the cited references are silent as to a method of suppressing HIV-induced cell fusion. Arfors, as discussed above, is related to

a method for perfusion therapy and, therefore is silent as to suppressing HIV-induced cell fusion. This missing teaching is not supplied by the other cited references. As discussed above, Springer, et al. describes methods relating to the use of proteins (but not antibodies) for treating an immune response mediated disorder such as allograft rejections, and is silent with respect to HIV-induced cell fusion. In addition, as discussed above, Pastan et al. relates to using immunotoxins to treat certain diseases by killing cells, and is silent with respect to suppressing HIV-induced cell fusion. Finally, regarding Hildreth et al., this reference is also silent with respect to blocking HIV-induced cell fusion. Accordingly, reconsideration and withdrawal of the rejection of claims 8, 9, 11-17, and 24-34 under 35 U.S.C. § 103(a) are respectfully requested.

D. Double Patenting Rejection

Claims 8-9, 11-17, and 24-34 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 7 of U.S. Patent No. 5,888,508. Filed herewith is a Terminal Disclaimer, disclaiming any term of a patent issuing from the subject application that may extend beyond the term of U.S. Patent No. 5,888,508. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 8-9, 11-17, and 24-34 under the judicially created doctrine of obviousness-type double patenting.

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: January 29, 2004

Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
Attorney for Applicant
Telephone No.: (858) 677-1456
Facsimile No.: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER NUMBER 28213